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DEPARTMENT OF HEALTH AND HUMAN SERVICES

Agency for Healthcare Research and Quality

Supplemental Evidence and Data for Systematic Reviews Request on Osteoarthritis of the Knee: An Update.

AGENCY: Agency for Healthcare Research and Quality (AHRQ), HHS.

ACTION: Request for supplemental evidence and data submissions.

SUMMARY: The Agency for Healthcare Research and Quality (AHRQ) is seeking scientific information submissions from the public. Supplemental datasets are being solicited to inform the review of *Osteoarthritis of the Knee: An Update,* which is currently being conducted by AHRQ's Evidence-based Practice Centers (EPC) Programs. Obtaining access to published and unpublished pertinent scientific information will improve the quality of this review. AHRQ is conducting this systematic review pursuant to section 902(a) of the Public Health Service Act, 42 U.S.C. 299a(a).

DATES: *Submission Deadline* on or before [INSERT DATE 30 DAYS AFTER DATE OF PUBLICATION IN THE FEDERAL REGISTER].

ADDRESSES:

E-mail submissions: SEADS@epc-src.org.

Print submissions:

Mailing Address:

Portland VA Research Foundation

Scientific Resource Center

ATTN: SEADS Coordinator

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FOR FURTHER INFORMATION CONTACT:

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SUPPLEMENTARY INFORMATION:

The Agency for Healthcare Research and Quality has commissioned its Evidence-based Practice Centers (EPC) Programs to complete a review of the evidence a review that updates information on treatments for osteoarthritis of the knee. The review will be titled *Osteoarthritis of the Knee: An Update*.

The EPC Program is dedicated to identifying as many studies as possible that are relevant to the questions for each of its reviews. In order to do so, AHRQ is supplementing the usual manual and electronic database searches of the literature by requesting information (e.g., details of studies conducted) from the public. We are looking for studies that report on treatments for osteoarthritis of the knee, including those that describe adverse events. The entire research protocol, including the key questions, is also available online at: https://www.effectivehealthcare.ahrq.gov/search-for-guides-reviews-and-reports/?pageaction=displayproduct&productID=2247.

This notice is to notify the public that the EPC program would find the following information on treatments for osteoarthritis of the knee helpful:

- A list of completed studies that your organization has sponsored for this indication. In the list, please *indicate whether results are available on ClinicalTrials.gov along with the ClinicalTrials.gov trial number*.
    - *For completed studies that do not have results on ClinicalTrials.gov*, please provide a summary, including the following elements: study number, study period, design, methodology, indication and diagnosis, proper use instructions, inclusion and exclusion criteria, primary and secondary outcomes, baseline characteristics, number of patients screened /eligible /enrolled /lost to follow-up /withdrawn /analyzed, effectiveness/efficacy, and safety results.
- *A list of ongoing studies that your organization has sponsored for this indication*. In the list, please provide the ClinicalTrials.gov trial number or, if the trial is not registered, the protocol for the study including a study number, the study period, design, methodology, indication and diagnosis, proper

use instructions, inclusion and exclusion criteria, and primary and secondary outcomes.

- Description of whether the above studies constitute all Phase II and above clinical trials sponsored by your organization for this indication and an index outlining the relevant information in each submitted file.

Your contribution is very beneficial to the EPC Program. The contents of all submissions will be made available to the public upon request. Materials submitted must be publicly available or could be made public. Materials that are considered confidential; marketing materials; study types not included in the review; or information on indications not included in the review cannot be used by the EPC Program.

This is a voluntary request for information, and all costs for complying with this request must be borne by the submitter.

The draft of this review will be posted on AHRQ's EPC program website and available for public comment for a period of 4 weeks. If you would like to be notified when the draft is posted, please sign up for the e-mail list at: https://effectivehealthcare.ahrq.gov/index.cfm/join-the-email-list1/.

The systematic review will answer the following questions. This information is provided as background. AHRQ is not requesting that the public provide answers to these questions. The entire research protocol, is available online at: https://www.effectivehealthcare.ahrq.gov/search-for-guides-reviews-and-reports/?pageaction=displayproduct&productID=2247

Key Questions:

Key Question 1

I. What is the clinical effectiveness of oral glucosamine and/or chondroitin, physical treatments, weight loss, oral serotonin-norepinephrine reuptake inhibitors (SNRIs), intraarticular corticosteroids and/or prolotherapy, topical or transdermal analgesics, acupuncture, or cell-based therapies in patients with primary or secondary OA of the knee, compared with appropriate placebo/sham controls or compared with other active interventions?

II. How do the outcomes of each intervention differ by the following population and study characteristics: sex, disease subtype (lateral, patellofemoral), severity (stage/baseline pain and functional status), weight status (body mass index), baseline fitness (activity level), comorbidities, prior or concurrent

treatments (including self-initiated therapies), and treatment duration or intensity?

Key Question 2

I. What harms are associated with each intervention in patients with primary or secondary OA of the knee?
II. How do the harms associated with each intervention differ by the following population or study characteristics: sex, disease subtype (lateral tibiofemoral, patellofemoral), severity (stage/baseline pain and functional status), weight status (body mass index), baseline fitness (activity level), comorbidities, prior or concurrent treatments (including self-initiated therapies), and treatment duration or intensity?

PICOTS (Population, Intervention, Comparator, Outcome, Timing, Setting)

Population(s)

I. Adults (age 18 or over) with a diagnosis of primary (or secondary) OA of the knee, as defined by the American Academy of Orthopaedic Surgeons (AAOS, 2013), ACR clinical classification criteria, or Kellgren-Lawrence stage.

II. Subpopulations of interest include those defined by sex, disease subtype (e.g., patellofemoral, or medial tibiofemoral), disease severity (stage/pain or functional status), body mass index, fitness/activity level, prior treatment, concurrent treatment(s), comorbidities

III. Exclusions:

A. Studies of individuals under age 18; those with OA caused by a congenital condition; and those with OA concomitant with a meniscal or anterior cruciate ligament tear will be excluded because these participants have conditions that differ importantly from the vast majority of OA patients

B. Studies that include those who have had knee replacement surgery on the affected limb or for whom outcomes will be measured after knee replacement surgery or who have concomitant joint disease such as rheumatoid arthritis or gout will be excluded because these conditions or procedures will confound assessment of the outcomes of interventions.

C. If three or more RCTs of a particular intervention are included that enroll at least 50 participants per study arm, smaller studies of the same intervention will be excluded unless they report on a subgroup analysis of interest because studies on management of OA of the knee that enroll fewer than 50

participants per study arm have been shown to have high risk of bias and significantly larger effect sizes.

Interventions

I. Pharmacologic treatments
    A. Oral agents
        i. Glucosamine and/or chondroitin
        ii. SNRIs (to be assessed for review in next update)
    B. Intra-articular injected agents (to be assessed for review in next update)
        i. Corticosteroids (to be assessed for review in next update)
        ii. Prolotherapeutic agents (e.g. dextrose) (to be reviewed in next update)
        iii. Hyaluronic acid (to be assessed for review in next update)
    C. Topical and transdermal agents (to be assessed for review in next update)
        i. Capsaicin (to be assessed for review in next update)
        ii. NSAIDs (to be assessed for review in next update)

II. Cell-based therapies
    A. Platelet-rich plasma

B. Intraarticular or arthroscopic administration of mesenchymal stem-cells or chondrocytes or tissue

C. Exclusions:

i. Phase I or II trials will not be included for efficacy, as the interventions are generally not FDA-approved for use.

III. Physical treatments and/or weight loss

A. Physical therapy and exercise programs

i. Manual therapy

ii. Land-based therapy and/or exercise

iii. Exercise programs (aerobic, resistance)

iv. Aquatherapy

v. Balneotherapy, mud therapy

vi. Heat or cold

vii. Self-management programs

B. Weight loss

C. Braces or kinesiology taping

D. Orthotic shoe inserts and/or wedges

E. Vibrating platform

F. Neuromuscular electrical stimulation (e.g., Transcutaneous electrical nerve stimulation)

IV. Acupuncture (to be assessed for review in next update)

A. Needle acupuncture alone (to be assessed for review in next update)
B. Moxibustion (to be assessed for review in next update)

V. Combination interventions (to be assessed for review in next update)
A. Sequential treatment algorithms (to be assessed for review in next update)

Comparators

I. Pharmacologic treatments: placebo-controlled or head-to-head non-inferiority only
II. Cell-based therapies: placebo- or sham-controlled only
III. Physical treatments and/or weight loss: placebo-controlled, usual care-controlled, or wait list-controlled only except for weight loss
IV. Neuromuscular electrical stimulation: sham stimulation without current
V. Wait list
VI. Treatment as usual
VII. Studies that use the untreated knee as a control will be excluded, based on evidence indicating that individuals with OA in one knee are likely to have some, but not necessarily identically,

reduced function in the other knee and that treatment of one knee only may improve pain in that knee but may not markedly improve function

VIII. Studies that use participants as their own controls will be excluded, unless no randomized controlled trials are identified for a particular intervention of interest, as quasi-experimental designs provide weaker evidence.

IX. Exclusions:

A. Studies that use an active control that has not been established to be effective will be excluded. Efficacy and effectiveness must be established before examining comparative effectiveness questions.

Outcomes

I. Short-term clinical outcomes

A. Pain (e.g., VAS, WOMAC, KOOS,)

B. Joint stiffness (WOMAC)

C. Function (WOMAC, Lequesne, others)

D. OARSI physical outcomes (e.g., timed up-and-go, 6-minute walk test,)

E. Patient Reported Outcome Measurement System (PROMIS®) and Osteoarthritis-Computer Adaptive Test (OA-CAT)

F. Inflammation or effusion

G. Medication use

II. Long-term clinical outcomes

A. Any of the short-term clinical outcomes

B. Instrumental activities of daily living (IADLs)

C. Quality of life (e.g., SF-36, EuroQuol EQ-5D, Arthritis Self-Efficacy scale, global assessment, patient satisfaction)

D. Surgery (i.e., rate of undergoing knee replacement)

III. Adverse effects of intervention(s)

IV. Outcome reporting

A. Only studies that report outcomes for knee OA alone

B. Mean differences at followup or percent of responders at followup will be abstracted

Timing

Minimum 1 month follow-up from initiation of treatment

Settings

Any setting

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